Patient Oriented Evidence That Matters:
2017: Important Studies That May Change Your Practice

Steven R. Brown, MD
Erik J. Lindbloom, MD
National Conference of Family Medicine Residents and Students
July 27-29, 2017

The amount of information in family medicine can be overwhelming for medical students and residents. Somehow, through this information jungle, learners need to be able to make cost-effective recommendations to their patients based on the best available evidence to benefit individual patients and the public health in a system with limited resources. Educators in family medicine have advocated for teaching information mastery to help tomorrow's family physicians become life-long learners.

Patient Oriented Evidence that Matters (POEMs) can help primary care physicians make cost-effective decisions and improve patient-centered care. POEMs should also be used to remove inequities in healthcare. Family physicians as information masters are the key to transforming health care.

A (very brief) introduction to information mastery:

- Usefulness= (Relevance x Validity)/Work
- Foreground and background information
- "PICO"
- POEMs vs. DOEs
- The evidence pyramid
- How do you find answers to questions? And how to you make sure important practice changers come to you even if you don't ask?
- Less is more. Become a healthy skeptic.

POEMs from the last year that could change your practice

#1: Ovarian cancer screening does not improve outcomes (UKCTOCS)

Clinical question: Do women who are screened for ovarian cancer have better health outcomes than women who are not screened?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Concealed
Setting: Population-based
Synopsis: In this British study, the researchers randomized more than 200,000 women between the ages of 50 years and 74 years to annual screening with pelvic ultrasound plus CA-125 testing, to ultrasound alone, or to no screening. Women were recruited through the National Health Service Trust registries. They used a modified intention-to-treat analysis to evaluate the rate of ovarian cancer mortality. The researchers followed the women up for a median of 11 years. At the end of that time, the rate of ovarian cancer detection was the same in each group (< 1%) and the ovarian cancer mortality rate was the same in each group (~ 0.3%). One could just stop there and conclude that screening is ineffective, as did the authors of the Prostate, Lung, Colorectal, Ovarian Cancer (PLCO) trial. Not these researchers. My guess is that they either had an agenda to push or were too embarrassed by spending 15 years and millions of dollars on a negative study. They went back and selectively excluded women who actually had oophorectomies or ovarian cancer and those who had exited the registry before randomization. Turns out these women were disproportionately distributed into the control group. Finally, after statistical modelling, they found that

there might be a delayed benefit in ovarian cancer mortality that is not evident until after 8 years. So, here we have a study with methods that stack the deck in favor of interventions (modified intention to treat, lack of masking, postrandomization exclusions, and so forth) that finds no statistical differences in outcomes. But after complex modelling and other data manipulations they find a possible delayed screening benefit on ovarian cancer mortality. No amount of data mining can overcome these biases. Oh, by the way-the authors report total mortality on page 23 of an appendix: no difference.
Bottom line: In this study (with methods that are biased in favor of the intervention), women who are screened for ovarian cancer are unlikely to experience any mortality benefit. (LOE = 1b-)
Reference: *Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet 2016;387(10022):945-956.*

#2: Dilute apple juice at least as good as electrolytes for children with mild gastroenteritis

Clinical question: Is oral hydration with dilute apple juice and preferred fluids noninferior to electrolyte maintenance solution in children with mild acute gastroenteritis?
Study design: Randomized controlled trial (single-blinded)
Funding source: Foundation
Allocation: Concealed
Setting: Emergency department
Synopsis: EMS is recommended for oral rehydration in children with gastroenteritis. However, it is relatively expensive and children frequently resist therapy because of the nasty taste (we had to freeze it into an ice pop to get our kids to take it). These investigators enrolled children, aged 6 months to 60 months, who presented to an ED in Canada with 3 or more episodes of vomiting or diarrhea in the preceding 24 hours; less than 96 total hours of symptoms; weight of 8 kg or more; and minimal dehydration (determined using a previously validated clinical dehydration scoring tool). Eligible children (N = 647) randomly received assignment (concealed allocation) to oral hydration in the ED with half-strength apple juice followed by preferred fluids (regular juices, milk, or sports beverages) or apple-flavored, sucralose-sweetened EMS. Color-matched, refrigerated solutions were pre-prepared in opaque, identical-appearing bottles to maintain masked outcome assessment. Following ED discharge, children continued to receive replacement therapy after each continued episode of vomiting or diarrhea with their assigned replacement fluid. Follow-up occurred daily by research nurses masked to treatment group assignment until the child remained asymptomatic for 24 hours. Complete follow-up occurred for 99.5% of participants. The primary outcome of treatment failure was a composite of any of the following occurring within 7 days of enrollment for hospitalization: intravenous rehydration, unscheduled physician encounter for persistent symptoms, protracted symptoms occurring after 7 days, a 3% or greater weight loss, and a clinically significant dehydration score. Using intention-to-treat analyses, the treatment failure rate for the primary outcome was significantly lower in the apple juice/preferred fluids group than in the EMS group (16.7% vs 25.0%; number needed to treat = 12.1; 95% CI 6.9-49.6). The benefit of apple juice/preferred fluids over EMS was most pronounced in children 24 months or older. The intravenous rehydration rate was also significantly lower in both the ED and overall after 7 days in children assigned to the apple juice/preferred fluids group than in the EMS group. Hospitalization rates were similar.
Bottom line: In this study performed in the emergency department (ED) of a major city in a high-income country, oral rehydration with half-strength apple juice followed by preferred fluids (ie, the same or other juices, milk, sports drinks) was at least as good if not better than apple-flavored electrolyte maintenance solution (EMS) for children, aged 6 months to 60 months, with mild acute gastroenteritis. (LOE = 1b)
Reference: *Freedman SB, Willan AR, Boutis K, Schuh S. Effect of dilute apple juice and preferred fluids vs. electrolyte maintenance solution on treatment failure among children with mild gastroenteritis. A randomized clinical trial. JAMA 2016:315(18):1966-1974.*

#3: Knee surgery does not reduce knee catching or locking in patients with meniscal tear (FIDELITY)

Clinical question: Does partial meniscectomy fix mechanical symptoms -- knee catching or locking -- better than sham surgery?
Study design: Randomized controlled trial (double-blinded)
Funding source: Foundation
Allocation: Concealed
Setting: Outpatient (specialty)
Synopsis: This report is a substudy of a larger study investigating the effect of arthroscopic surgery on (relatively) young patients with meniscal tear but without signs of osteoarthritis. These Finnish investigators enrolled 146

patients, aged 35 to 65 years, who had knee pain for at least 3 months and evidence of a degenerative meniscal tear but did not respond to conservative treatment. They excluded patients with a verified locked knee (unable to straighten), though they included patients (n = 69) who had symptoms of "catching" or occasional or frequent locking. All patients underwent arthroscopic surgery, though slightly more than half were randomly assigned, using concealed allocation, to a group that did not have the tear addressed (sham surgery). In the surgery group, damaged and loose parts were removed; in the sham surgery group, diagnostic arthroscopy was performed and the surgeon simulated actual surgery (since patients were awake) without removing anything. In the subsequent 12 months, 23 (72%) in the surgery group and 22 (59%) in the sham surgery group with preoperative mechanical symptoms reported symptoms at least once. Only 9 of 32 patients (28%) in the surgery subgroup and 15 of 37 (41%) in the sham surgery subgroup reported complete resolution of their symptoms.
Bottom line: I guess it's time to stop the knee-jerk reaction of sending patients with occasional catches and locking to ortho for meniscal resection. Removing the torn bits of meniscus in middle-aged patients who have intermittent knee catches or locking does not decrease their likelihood of experiencing symptoms in the following year as compared with diagnostic arthroscopy (ie, looking but not touching). In general, meniscectomy does not improve knee pain, regardless of the symptoms (N Engl J Med 2013;369(26):2515-24). (LOE = 1b-)
Reference: *Sihvonen R, Englund M, Turkiewicz A, Jarvinen TL, for the Finnish Degenerative Meniscal Lesion Study Group. Mechanical symptoms and arthroscopic partial meniscectomy in patients with degenerative meniscus tear: A secondary analysis of a randomized trial. Ann Intern Med. 2016;164(7):449-455.*

#4: Single-dose dexamethasone = 3 days of steroids in children with acute asthma

Clinical question: In children with acute exacerbation of asthma, is a single dose of corticosteroid as effective as 3 days of treatment?
Study design: Randomized controlled trial (nonblinded)
Funding source: Foundation
Allocation: Uncertain
Setting: Emergency department
Synopsis: These Irish investigators enrolled 226 children (for a total of 245 enrollments; some were enrolled twice) between the ages of 2 and 16 years with an acute exacerbation of asthma. The children were randomized (concealed allocation unknown) to receive either a single dose of oral dexamethasone (0.3 mg/kg) or 3 days of oral prednisolone (1 mg/kg/day) in addition to usual therapy. None of the patients, their parents, or the investigators were masked to treatment assignment, though the outcome assessor was unaware of treatment at the time of evaluation, which was 4 days after presentation. The Pediatric Respiratory Assessment Measure (PRAM) was used to measure symptoms. It consists of measuring suprasternal and scalene muscle contraction, air entry, wheezing, and oxygen saturation, with a maximum score of 12. At 4 days, PRAM scores were similar among the 2 groups (0.91 vs 0.91). Hospital admission rates were also similar between the 2 groups, as were days lost from school and parental workdays missed. Return visits were similar between the 2 groups, though more children receiving the single dose required further steroid treatment within the following 2 weeks (13% vs 4%). Vomiting occurred more often with prednisolone.
Bottom line: In addition to usual beta-agonist treatment, a single dose of oral dexamethasone is as effective as 3 days of prednisolone (with less vomiting) in decreasing respiratory symptoms without increasing hospitalizations, follow-up visits, and days lost from school. Additional treatment with a steroid was more common in the group receiving the single dose of dexamethasone. (LOE = 1b)
Reference: *Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. Ann Emerg Med. 2016;67(5):593-601.*

#5: Stop using antipsychotics to treat or prevent delirium -- they are no better than placebo

Clinical question: Are antipsychotic medications effective in preventing or treating delirium in hospitalized patients?
Study design: Meta-analysis (other)
Funding source: Foundation
Setting: Inpatient (any location)
Synopsis: These authors searched several databases and a clinical trials registry to identify randomized trials and cohort studies that evaluated the use of antipsychotic medications for preventing or treating delirium in hospitalized adults. Two authors independently evaluated each study for inclusion and assessed the risk for bias among the included studies. One author adjudicated disagreements and also independently assessed a random 10% subsample of all articles. The authors excluded studies that focused exclusively on patients with dementia or substance withdrawal. They ultimately included 19 studies: 7 evaluated delirium prevention after surgery and 12 evaluated delirium treatment in medical and surgical patients. Six of the prevention studies and 10 of the treatment studies were randomized trials. Three of the prevention studies and 3 of the treatment studies were at low risk of bias. The studies

were relatively small, including between 28 and 496 patients. In the prevention studies, the rate, duration, and severity of delirium were similar between those treated with antipsychotics and those in the control group. Additionally, the authors found no difference in the hospital lengths of stay or intensive care unit lengths of stay between patients receiving antipsychotics and patients in the control group. Finally, the authors found no difference in mortality. In addition to searching a clinical trials database, the authors report their formal evaluation detected no publication bias. Finally, the authors detected moderate to high levels of heterogeneity among the various outcomes.
Bottom line: The available data indicate that antipsychotic medications are ineffective in preventing or treating delirium in hospitalized patients. Since there are concerns about falls and extrapyramidal effects with antipsychotics (not reported in this study), we should stop using them. Just say no. (LOE = 1a-)
Reference: *Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. J Am Geriatr Soc 2016;64(4):705-714*

#6: Updated CDC guidelines for opioid prescribing for chronic pain

Clinical question: How should primary care clinicians handle opioid prescribing for adults with chronic pain not caused by cancer?
Study design: Practice guideline
Funding source: Government
Setting: Various (guideline)
Synopsis: Prescription opioid use has increased significantly over the last decade and decreasing opioid-related morbidity is an important public health goal. These authors collected the available evidence on opioid treatment for chronic noncancer pain to answer questions about opioid initiation and follow up, opioid selection and continuation, and opioid harms. The evidence search, along with input from topic experts, professional societies, and federal advisory committees, generated a list of best practice recommendations. The overall quality of evidence was poor. Salient points from the guideline include: (1) Recommending nonpharmacologic therapies (eg, exercise therapy) and nonopioid pharmacologic therapies (NSAIDs, antidepressants, and anticonvulsants) as first-line therapies for chronic pain; (2) establishing realistic goals for improvements in pain and function prior to initiation; (3) discussing known risks and benefits of opioids prior to initiation; (4) initiating therapy with immediate-release preparations and avoiding extended-release preparations; (5) using the lowest effective daily dose with careful reexamination of the risks and benefits of continued therapy (preferably with the help of a pain specialist) when doses exceed 50 to 90 morphine milligram equivalents per day; (6) ensuring close follow-up (1-4 weeks) after initiation and dosing changes, with periodic evaluation (1-3 months) for patients taking stable doses; and (7) using risk mitigation tools, including prescription-drug monitoring programs (all patients), urine drug screens, and naloxone education for patients at increased risk of adverse outcomes. Most studies of opioid effectiveness have been limited to study periods of 6 weeks to 3 months and no studies have evaluated effectiveness for longer than 1 year. Please attribute the authorship of this POEM to Patrick L. Turner, MD, Fellow, Department of Family Medicine, The University of Virginia, Charlottesville, VA.
Bottom line: Based on low-quality evidence, primary care clinicians should carefully weigh the decision to initiate chronic opioid therapy and establish realistic treatment goals focused not on pain relief but on functional improvement. The lowest effective dose should be used concomitantly with risk mitigation strategies to minimize adverse outcomes. Multidisciplinary treatment teams are highly encouraged for patients with an increased risk of adverse events. However, time constraints will likely make effective implementation difficult in current real-world clinical environments. (LOE = 5)
Reference: *Dowell D, Haegerich T, Chou R. CDC guideline for prescribing opioids for chronic pain - United States, 2016. JAMA 2016;315(15):1624-1645.*

#7: CBT effective in adolescents with depression who don't want medication

Clinical question: Is cognitive behavioral therapy effective for adolescents with depression who decline antidepressant drug treatment?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Uncertain
Setting: Outpatient (primary care)
Synopsis: These researchers identified potential patients by mailing study brochures to parents of adolescents 12 to 18 years of age who had a recent prescription for an antidepressant (from a health maintenance organization in the United States) that went unfilled or was initially dispensed but not refilled. In other words, the patients did not fail antidepressant therapy but simply chose not to begin (or continue) it. The 212 adolescents who had major depressive disorder were randomized (allocation concealment uncertain) to continue treatment as usual (as determined by their primary care provider) or treatment as usual plus at least 4 sessions of CBT aimed at addressing unrealistic thinking

and increasing pleasant activities (behavioral activation). The patients could continue a second set of 4 to 6 sessions, if desired, and most did. Recovery, defined as at least 8 weeks of well time as measured by the Children's Depression Rating Scale—Revised, occurred significantly faster in the CBT group and was significantly more likely in the first year but not the second year of follow-up. Quality of life was better with therapy in the first year after therapy but not in the second year. Hospital admissions for psychiatric diagnoses were significantly higher in the control group. Substance use, suicidal behavior, and parent-reported outcomes were not different between the 2 groups, but the study may not have been long enough to find a difference if one exists. These results jibe with the results of several meta-analyses examining the effect of cognitive behavioral therapy for adolescents with depression.
Bottom line: In adolescents who eschew drug treatment of major depression, short-term cognitive behavioral therapy (CBT) is more effective than treatment as usual in inducing recovery, with a number needed to treat of 4 to 10. CBT also produced faster results. (LOE = 1b)
Reference: *Clarke G, DeBar LL, Pearson JA, et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: A randomized trial. Pediatrics 2016;137(5):e20151851.*

#8: CVD risk calculator overestimates risk

Clinical question: Does the American College of Cardiology/American Heart Association Pooled Cohort Risk equation accurately predict cardiovascular risk in a typical cohort of patients?
Study design: Decision rule (validation)
Funding source: Foundation
Setting: Population-based
Synopsis: These US investigators identified a target population of 307,591 patients, 40 years to 75 years old, from a large integrated health care delivery system, for consideration of cholesterol-lowering therapy in 2008. The follow up lasted through 2013. The authors excluded people with known ASCVD, diabetes mellitus, low-density lipoprotein cholesterol levels of less than 70 mg/dL (1.8 mmol/L) or greater than 190 mg/dL (4.9 mmol/L), and those receiving lipid-lowering therapy. They also excluded from the results people with incomplete 5-year follow-up. Though the majority of the patients were white, 7.2% were black, 17.2 were Asian/Pacific Islander, and 6.1% were Hispanic. The average patient age was 54.8 years, 61.6% were women, 28% were obese, and 33% were treated with medication for hypertension. Using the Pooled Cohort Risk Equation, 31% would have qualified for lipid-lowering treatment (ie, a 10-year risk of at least 7.5%). Over 5 years, the actual incidence of ASCVD increased linearly each year but did not approach the rates calculated by the equation for the same 5-year period. In a separate analysis, risk calculations for patients with diabetes similarly overestimated risk. These results line up with the results from other studies that have attempting to validate the risk equation.
Bottom line: This risk calculator substantially overestimates the actual occurrence of atherosclerotic cardiovascular disease (ASCVD) events over 5 years in a typical multiethnic population. The risk calculator estimates 10-year risk, but the authors extrapolated the equation to 5 years and compared the results since the risk increase seems to be linear. As has been pointed out before, this frequently used risk calculator substantially overestimates the percentage of patients who will benefit from lipid-lowering treatment. (LOE = 1b)
Reference: *Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. J Am Coll Cardiol 2016;6(18):2118-2130.*

#9: Hospital program that emphasizes walking improves postdischarge mobility

Clinical question: Can a hospital-based mobility program improve posthospitalization function and mobility?
Study design: Randomized controlled trial (single-blinded)
Funding source: Government
Allocation: Concealed
Setting: Inpatient (any location) with outpatient follow-up
Synopsis: Low mobility during hospitalization may lead to functional decline, especially in older adults. In this study, investigators randomized patients 65 years or older in the medical wards of a Veterans' Affairs Medical Center to an in-hospital mobility program (n = 50) or to usual care (n = 50). Included patients were ambulatory in the 2 weeks prior to admission and did not have delirium or dementia. In the mobility group, research assistants went on scheduled walks with patients for 15- to 20-minute sessions up to twice daily. Patients were also encouraged to set daily goals to stay out of bed as well as discuss any mobility barriers that they were experiencing. The usual care group also received twice daily visits from the research assistants but did not participate in the formal mobility program. The 2 groups had similar baseline characteristics: almost all patients were male, their mean age was 74 years, and their mean length of stay was 4 days. The mobility group completed 122 of a potential 238 scheduled walks (51%); the main reasons for lack of completion were patient refusal and lack of availability of patient or staff. To assess functional outcomes, patients in both groups were asked to rate their ability to perform 7 basic ADLs at different time points in the study, including 2 weeks prior to admission using the Katz scale. There were no significant differences detected in self-reported summary ADL scores between the 2 groups prior to admission, at admission, at discharge,

or at 1 month postdischarge. Additionally, the Life-Space Assessment (LSA) score was used to assess patients at admission and at 1 month posthospitalization. This score measures community mobility (range = 0 – 120, with higher scores indicating greater mobility) based on patients' reports of distance moved during the preceding 4 weeks of the assessment. Although the 2 groups had similar LSA scores at baseline, the mobility group maintained their LSA scores at 1 month posthospitalization while the usual care group's score declined by 10 points from baseline (admission scores: 54 in mobility group vs 52 in usual care group; posthospitalization scores: 53 in mobility group vs 42 in usual care group; P = .02). Adjusted analyses confirmed these findings.
Bottom line: Patients in the hospital spend a lot of time in bed. In this small study, a hospital-based mobility program incorporated scheduled walks and behavioral interventions to encourage time spent out of bed for older patients during their hospital stay. As compared with patients who received usual care, patients in the mobility program were more likely to maintain their status quo with regard to community mobility following discharge. Although there was no effect seen on functional outcomes as measured by performance on activities of daily living such as bathing and dressing, the patients in this study were fairly independent to start. (LOE = 1b)
Reference: *Brown CJ, Foley KT, Lowman JD Jr, et al. Comparison of posthospitalization function and community mobility in hospital mobility program and usual care patients. JAMA Intern Med 2016;176(7):921-927.*

#10: Some adults should take aspirin to prevent CVD, colorectal cancer

Clinical question: Should adults take aspirin to lower the risk of cardiovascular disease and colorectal cancer?
Study design: Practice guideline
Funding source: Government
Setting: Various (guideline)
Synopsis: Citing 5 new studies of aspirin to prevent CVD and additional analysis of data on colorectal cancer, the USPSTF has updated and refined its recommendations for recommending aspirin to decrease the likelihood of both CVD and colorectal cancer. They conclude that for adults aged 50 to 59 years there is a moderate chance of a reduction in risk of myocardial infarction and ischemic stroke after 10 years of use and, with long-term use, a reduced incidence of colorectal cancer. In contrast, there is a small risk of gastrointestinal bleeding in this age group. The group suggests the use of the American College of Cardiology/American Heart Association risk calculator (see Essential Evidence Plus or http://tools.acc.org/ASCVD-Risk-Estimator/), though this calculator is likely to overestimate risk—and, therefore, the benefit of aspirin in many people (see J Am Coll Cardiol 2016;67:2118-2130). For patients aged 60 to 69 years with a 10% or greater CVD risk, the USPSTF suggests the decision be based on the desires of the patient (C recommendation). The evidence is insufficient regarding the use of aspirin for people younger than 50 years or older than 70 years of age (I recommendation).
Bottom line: The U.S. Preventive Services Task Force (USPSTF) recommends that adults aged 50 years to 59 years take 81 mg aspirin per day to prevent both cardiovascular disease (CVD) and colorectal cancer if they meet the following criteria: (1) 10% or greater CVD risk, (2) no increased risk for bleeding, (3) a life expectancy of at least 10 years, and (4) a willingness to continue treatment for at least 10 years. This is a B recommendation (should be offered to individuals meeting the criteria). (LOE = 5)
Reference: *Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016;164(12):836-845.*

#11: Getting an infant to sleep: graduated extinction and sleep fading are effective

Clinical question: Which method of getting your infant to sleep causes less stress in infants and parents?
Study design: Randomized controlled trial (single-blinded)
Funding source: Foundation
Allocation: Concealed
Setting: Outpatient (primary care)
Synopsis: This study included 43 infants aged 6 months to 16 months (63% girls) and their parents who were initially assigned to 1 of 3 methods to get the infant to sleep. After a 1-week observation period to collect baseline data, the families were then randomized, using concealed allocation, into 1 of 3 groups: (1) graduated extinction, in which the parent puts the child in bed while still awake and waits before checking on the child, initially for 2 minutes, then 4 minutes, and then 6 minutes (in the same night); (2) sleep fading, in which the children were put to bed 15 minutes later than normal; if still awake 15 minutes later, they were put to bed 30 minutes later the following night; and (3) control, in which parents only received general information about infant sleep. Both interventions, as compared with the control group, resulted in decreased time to sleep and number of awakenings. Maternal stress, measured by a survey questionnaire, moderately decreased over the first month of the intervention. Infant stress, measured by interviewing the infant (just kidding; they measured salivary cortisol levels), was slightly lower in the infants in the treatment groups. The security of child-parent attachment was not different among the treatment groups.

Bottom line: Getting an infant to sleep, a problem aptly illustrated in the wildly successful book Go the F**k to Sleep (the Samuel L. Jackson–read version on YouTube is hilarious), is what turns mere mortals into parents. This study found that "graduated extinction" (increasing intervals between comforting the infant) and "sleep fading" (putting the child to bed progressively later until you find the sweet spot) are both effective at decreasing sleep latency and the number of awakenings and decreasing maternal and infant stress. Neither approach affected the likelihood of secure child–parent attachment. (LOE = 1b-)
Reference: *Gradisar M, Jackson K, Spurrier NJ, et al. Behavioral interventions for infant sleep problems: A randomized controlled trial. Pediatrics 2016;137(6):e20151486.*

#12: Hypertensive urgency not really an urgent problem

Clinical question: How urgently should we aim to control hypertensive urgency?
Study design: Cohort (retrospective)
Funding source: Self-funded or unfunded
Setting: Outpatient (any)
Synopsis: These authors identified all patients in a single healthcare system (N = 58,535) who presented to an office or emergency department with a blood pressure of at least 180 mm Hg systolic and/or 110 mm Hg diastolic. Most of the patients in the analysis just met these minimums; only 10.2% had a systolic pressure of 200 mm Hg or higher and 5.7% had a diastolic pressure of 120 mm Hg or higher. The mean age of the patients was 63.1 years, 57.7% were women, and 76% were white. A small proportion (0.7%) were hospitalized for blood pressure management; however, half of these patients had pressures of at least 200 mm Hg systolic or at least 120 mm Hg diastolic. Regardless of treatment or place of treatment, both the likelihood of blood pressure control and the likelihood of adverse effects were low. At 1 month, less than 15% of patients had controlled blood pressure; at 6 months, less than 40% had controlled blood pressure. Even so, the likelihood of a major adverse cardiovascular event was low in the next 7 days (0.1%), at 8 to 30 days (0.2%), or within 6 months (0.9%). Hospitalization was not associated with a decrease in the risk of adverse outcomes.
Bottom line: It seems that rapid treatment of patients with hypertensive urgency is both unsuccessful and unnecessary. In this study of almost 60,000 patients, 80% did not have controlled blood pressure (< 140/< 90 mm Hg) after 1 month of treatment, including patients who were hospitalized. On the other hand, the risk of a major cardiovascular event was also low: 1 in 1000 over the next 7 days. (LOE = 2b)
Reference: *Patel KK, Young L, Howell EH, et al. Characteristics and outcomes of patients presenting with hypertensive urgency in the office setting. JAMA Intern Med 2016;176(7):981-988.*

#13: ACP chronic insomnia guideline: CBT before drugs

Clinical question: How should chronic insomnia be managed?
Study design: Practice guideline
Funding source: Self-funded or unfunded
Setting: Various (guideline)
Synopsis: This guideline addresses the treatment of chronic insomnia, defined as a sleep disorder that causes significant functional distress or impairment at least 3 nights a week for 3 months. The recommendations are based on a systematic review of treatment options. Based on moderate-quality evidence, cognitive behavioral therapy aimed at insomnia improved remission, treatment response, time to sleep, waking after sleep onset, and sleep quality. Treatment can be delivered as individual or group therapy, by telephone, web-based, or via self-help books. Harm with therapy may occur but has not been reported in studies. Cognitive behavioral therapy for insomnia consists of: (1) Cognitive therapy aimed at dysfunctional beliefs and attitudes toward sleep and insomnia; (2) stimulus control: avoiding nonsleep activities in the bedroom; (3) sleep restriction: limiting time in bed to match perceived sleep duration to assure that more than 85% of time spent in bed was spent sleeping; (4) sleep hygiene: typical measures of alcohol, caffeine, and nicotine intake and sleep scheduling; and (5) relaxation techniques: meditation, mindfulness, and so forth. Drug therapy using newer hypnotics—eszopiclone (Lunesta), zolpidem (Ambien), and suvorexant (Belsomra)—improves some aspects of sleep, though most studies of these drugs were of low quality. Benzodiazepine hypnotics have not been studied for long-term use. Doxepin, in a low-quality study, was shown to improve total sleep time and waking after sleep onset, but other older medicines, such as diphenhydramine and trazodone, have not been studied. Drug treatment was judged to be second-line therapy because of its cost and harms. This group suggests using medicine for no longer than 4 to 5 weeks, if possible.
Bottom line: Based on a systematic review of randomized trials, the American College of Physicians recommends cognitive behavioral therapy as initial treatment for insomnia, reserving pharmacologic therapy as second-line treatment after a discussion of benefits and risks with the patient. Unfortunately, the guideline does not present the data in a way that would facilitate this discussion. (LOE = 5)

Reference: *Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD, for the Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: A clinical practice guideline from the American College of Physicians. Ann Intern Med 2016;165(2):125-133.*

#14: Chocolate consumption may make acne vulgaris worse

Clinical question: Oh no! Does eating chocolate really cause more pimples?
Study design: Cross-over trial (randomized)
Funding source: Self-funded or unfunded
Allocation: Uncertain
Setting: Outpatient (any)
Synopsis: Many a teenager has been torn between the desire to consume a delicious hunk of chocolate and the worry that it worsens acne. These investigators enrolled 54 consenting college students with acne vulgaris who agreed to abstain completely from chocolate consumption for the duration of the study. No information is provided on the baseline severity of acne but each participant provided a prestudy facial photo to allow lesion counting. Study participants randomly received (uncertain allocation concealment) a standard size Hershey's milk chocolate bar or 15 Jelly Belly jelly beans in order to provide an equal amount of glycemic load to each intervention group. Acne changes were assessed by a second facial photographic review 48 hours later by a dermatologist masked to intervention group assignment. After a 4-week washout period, study subjects received the opposite intervention from what they had in the first phase of the study (crossover design) and again had a facial photographic assessment performed before and 48 hours after the intervention. No statistically significant group differences were noted in the number of acne lesions at baseline in both study phases. After each intervention, however, the chocolate consumption group had a statistically significant increase in acne lesions compared with the jelly bean group (+4.8 vs -0.7 lesions, respectively). Adverse effects included a strong desire for continued ingestion of the intervention material, which was shared by both the study participants and personnel (as well as the author and editor of this review).
Bottom line: It looks like it's true after all! This study found a statistically significant increase in facial acne lesions among college students 48 hours after ingesting chocolate instead of jelly beans (average compared with baseline: 4.8 new lesions vs 0.7 fewer lesions, respectively). (LOE = 1b-)
Reference: *Delost GR, Delost ME, Lloyd J. The impact of chocolate consumption on acne vulgaris in college students: A randomized crossover study. J Am Acad Dermatol 2016:75(1):220-221.*

#15: CPAP doesn't reduce cardiovascular events (RICCADSA)

Clinical question: Does continuous positive airway pressure decrease events in nonsleepy patients with obstructive sleep apnea and coronary artery disease?
Study design: Randomized controlled trial (single-blinded)
Funding source: Industry + govt
Allocation: Uncertain
Setting: Outpatient (any)
Synopsis: This study included patients with recent coronary artery percutaneous interventions or bypass grafting who also had obstructive sleep apnea. The authors also included patients with an apnea hypopnea index of less than 5 per hour as a secondary control group (the target group had at least 15 per hour). All patients needed to not be sleepy (Epworth Sleepiness Scale score < 10). The patients were randomized to receive either autotitrating CPAP (n =122) or no CPAP (n = 122). The researchers used intention to treat to analyze a fruit-salad composite outcome of repeat revascularization, myocardial infarction, stroke, and cardiovascular mortality. They obtained these outcomes from national databases and medical record systems. After a median of nearly 6 years of follow up, 7 patients treated with CPAP died compared with 9 treated with no CPAP. Only 49 patients achieved the composite end point, with no significant difference between treatment groups. We all know that CPAP is not a particularly comfortable device so adherence can be an issue. When the researchers looked at those patients who used CPAP for less than 3 hours per night, they still saw no difference in outcomes. However, those using CPAP for more than 4 hours per night had a slight decrease in the rate of cardiovascular events. Recall that "on treatment" outcomes tend to be biased in favor of interventions. Finally, the study was powerful enough to detect modest differences in the rate of the composite outcome.
Bottom line: Overall, the use of continuous positive airway pressure (CPAP) in nonsleepy patients with obstructive sleep apnea and coronary artery disease does not have a meaningful effect on cardiovascular events. We recently reviewed trials that showed CPAP has no meaningful effect on diabetes control, either. These papers all formally tested associations between sleep apnea and various bad outcomes and failed to find that treating the sleep disorder did anything other than treat the sleep disorder. (LOE = 2b)
Reference: *Peker Y, Glantz H, Eulenburg C, Wegscheider K, Herlitz J, Thunstrom E. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA Randomized Controlled Trial. Am J Respir Crit Care Med. 2016;194(5):613-620.*

#16: Fast clean-catch urine procedure works more than half the time for infants

Clinical question: Is there a way to quickly obtain a clean-catch urine sample from infants without catheterization or suprapubic aspiration?
Study design: Cohort (prospective)
Funding source: Self-funded or unfunded
Setting: Emergency department
Synopsis: These researchers conducted the study in a pediatric emergency department in Canada by enrolling a convenience sample of 126 male and female infants younger than 6 months of age who needed a urine sample. A total of 9% of of these infants would be found to have a urinary tract infection. Here is the fast clean-catch procedure: After giving infants the opportunity to feed for 20 minutes, the genital area was cleaned and infants were held under their armpits by a parent, legs dangling in males and hips flexed in females. The infant was gently tapped in the suprapubic area at a frequency of 100 taps per minute for 30 seconds, followed by lumbar paravertebral massage maneuvers for 30 seconds. These 2 stimulation maneuvers were repeated until micturition began or for a maximum of 5 minutes. On average, this process was effective in 49% of the infants, producing a sample in a median time of 45 seconds. It was more effective in children younger than 3 months (58%) than older infants (26%). Contamination occurred in 16% of samples.
Bottom line: In infants younger than 3 months, a quick noninvasive method of collecting clean-catch urine will be effective more than half the time. The process involves feeding, followed by exposure to air and gentle suprapubic tapping alternating with lumbar massage (see Synopsis for complete description). In the infants who will urinate during this procedure, half of them will do so in 45 seconds or less. Contamination will occur in approximately 1 in 6 samples. (LOE = 3b)
Reference: *Labrosse M, Levy A, Autmizguine J, Gravel J. Evaluation of a new strategy for clean-catch urine in infants. Pediatrics 2016;138(3):e20160573.*

#17: No difference in topical steroids on wet or dry skin of children with atopic dermatitis

Clinical question: Is it more effective to apply topical steroids to wet skin or dry skin of children with atopic dermatitis?
Study design: Randomized controlled trial (single-blinded)
Funding source: Foundation
Allocation: Concealed
Setting: Outpatient (specialty)
Synopsis: Clinicians commonly recommend the application of topical steroids to presoaked, wet skin in children with AD to enhance drug absorption. These investigators identified 45 children, aged 2 weeks to 18 years, who met standard clinical diagnostic criteria for AD. Eligible patients randomly received (concealed allocation assignment) instructions to apply topical steroids twice daily (triamcinolone acetonide 0.1% ointment for patients 2 years or older or hydrocortisone 2.5% ointment for patients younger than 2 years). Children in the soak-and-smear group initially soaked in a bath of plain lukewarm water for 10 minutes, followed by immediate application of the corticosteroid ointment. Patients in the control group applied the topical steroid to dry skin only. Individuals masked to treatment group assignment assessed the outcomes using a standard eczema severity scoring tool. Complete follow-up occurred for all 45 children at 14 days. Using intention-to-treat analysis, both groups showed similar improvement scores for disease severity, with the soak-and-smear and control groups showing an 84.8% and 81.4% reduction in eczema severity scores, respectively (P = NS). No significant difference occurred in adverse events. The study was 80% powered to detected a predetermined clinically significant difference between the 2 treatment groups.
Bottom line: This small study found no difference in the efficacy or tolerability of topical steroids applied to wet skin versus dry skin of children with atopic dermatitis (AD). (LOE = 1b)
Reference: *Kohn LL, Kang Y, Antaya RJ. A randomized, controlled trial comparing topical steroid application to wet versus dry skin in children with atopic dermatitis (AD). J Am Acad Dermatol 2016;75(2):306-311.*

#18: Harms per 100,000 colonoscopies: 50 perforations, 260 bleeds, and 3 deaths

Clinical question: What are the harms of colonoscopy?
Study design: Meta-analysis (other)
Funding source: Self-funded or unfunded
Setting: Population-based
Synopsis: These authors performed a systematic review of population-based studies published since 2001 that reported complication rates in the 30 days following colonoscopy. Both screening and diagnostic/surveillance studies were included. Bleeding was defined as a bleeding complication requiring intervention, a visit to the emergency

department, or hospitalization. The authors searched PubMed, Cochrane, and EMBASE databases, and ultimately identified 21 studies reporting the outcomes of nearly 2 million colonoscopies. The data for perforation and bleeding were stratified by colonoscopies that included a polypectomy and those that did not. In general, complication rates were higher for patients undergoing colonoscopy for symptoms compared with those undergoing screening colonoscopy (perforation: 1.3 vs 0.3 per 1000; bleeding: 4.6 vs 2.4 per 1000). The risk of complications was also higher for patients undergoing polypectomy than in those with no polypectomy (perforation: 0.8 vs 0.4; bleeding: 9.8 vs 0.6). The mortality rate was only 3 per 100,000 colonoscopies. The likelihood of a perforation or death seems to be stable over time, while the risk of bleeding is declining (from 6.4 to 1.0 episodes per 1000 colonoscopies).
Bottom line: Overall, the harms per 100,000 colonoscopies were 50 perforations, 260 bleeds, and 3 deaths. Among patients undergoing screening colonoscopy, the likelihood of a bleeding complication was 240/100,000 and the likelihood of a perforation was 30/100,000. (LOE = 1a)
Reference: *Reumkens A, Rondagh EJ, Bakker CM, Winkens B, Masclee AA, Sanduleanu S. Post-colonoscopy complications: a systematic review, time trends, and meta-analysis of population-based studies. Am J Gastroenterol 2016;111(8):1092-1101.*

#19: Individual and organizational approaches can ease physician burnout

Clinical question: What strategies are effective in easing physician burnout?
Study design: Meta-analysis (other)
Funding source: Foundation
Setting: Various (meta-analysis)
Synopsis: Nearly half of all physicians experience at least one symptom of burnout, though rates vary greatly among specialties. Characterized by emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment, burnout has been associated with medical errors, diminished engagement, adverse personal health, and departure from practice. These authors systematically reviewed multiple databases and registries, and references of relevant studies and past reviews, to identify studies reporting the outcomes of interventions to prevent and reduce physician burnout. They included pretty much any comparative study, including nonrandomized trials and before/after studies, as long as the original authors used validated instruments to assess burnout, emotional exhaustion, or depersonalization. Two reviewers independently assessed articles for potential inclusion and methodologic quality. They resolved discrepancies by consensus. They anticipated significant heterogeneity so the authors used conservative approaches to estimating the effects of the interventions. Ultimately, they included 15 randomized trials with 716 physicians, and 37 observational studies with 2914 physicians. Among the randomized trials, 3 addressed organizational changes (eg, work intensity, changes in work processes) and 12 addressed individual approaches (eg, self-care, stress management, mindfulness). Among the 37 observational studies, 17 involved structural interventions and 20 focused on the individual. In the randomized trials, the interventions had no effect on overall burnout or depersonalization scores, but slightly reduced emotional exhaustion scores. Among the observational studies, the overall burnout and emotional exhaustion scores improved, but the depersonalization scores did not. When the authors pooled all studies, overall burnout, emotional exhaustion, and depersonalization scores improved. The authors note that a 1-point change in burnout scores is associated with a meaningful difference in self-perceived major medical errors and suicidal ideation. Finally, among the randomized trials, the authors report the absolute rate of burnout was 54% in control groups compared with 44% in the intervention groups (number needed to treat [NNT] = 10; 95% CI 8 - 20). High emotional exhaustion decreased from 38% to 24% (NNT = 7; 6 - 9) and high depersonalization minimally decreased from 38% to 34% (NNT = 25).
Bottom line: In this systematic review, individual and organizational approaches can prevent and reduce physician burnout, improve emotional exhaustion, and slightly decrease depersonalization. (LOE = 2a-)
Reference: *West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis. Lancet 2016;388(10057):2272-2281.*

#20: Placebo plus message of benefit decreases chronic low back pain

Clinical question: Can simply telling patients that a medicine works, even if it is placebo, decrease pain and improve disability in patients with chronic low back pain?
Study design: Randomized controlled trial (nonblinded)
Funding source: Government
Allocation: Concealed
Setting: Outpatient (any)
Synopsis: These investigators, who conducted the study in Portugal, enrolled 83 patients who'd had low back pain for at least 3 months and responded to an advertisement. Most (87%) were taking analgesia, approximately 40% were taking adjuvant medication (eg, gabapentin or a muscle relaxant), and approximately 20% were taking an antidepressant. The authors excluded patients with severe fibromyalgia or rheumatoid arthritis and those who had received opioid treatment in the past. For 3 weeks patients were asked to continue their usual treatment. Using

concealed allocation, half of the patients were also given 2 placebo tablets twice a day. They were told that it was an inactive placebo, but: (1) it could still have a powerful effect; (2) the body can automatically respond to placebo; (3) a positive attitude is helpful but not necessary; and, (4) the placebo must be taken faithfully. Knowingly taking placebo significantly decreased maximum reported pain, minimum reported pain, and usual pain as compared with usual therapy only. Back pain–related disability was also decreased with placebo. There were several problems with the study, however: unbalanced baseline pain, small numbers in each group, and the lack of a co mmercially available placebo.
Bottom line: Building on the received wisdom of Sir William Osler that, "The desire to take medicine is perhaps the greatest feature which distinguishes man from animals," these investigators gave twice daily placebo to patients with chronic back pain and told them it was placebo. They also told them that placebos can have a pronounced effect (which is true). The addition of placebo to usual care improved patients' pain and disability scores over the 3 weeks of the study. Although we probably won't start prescribing placebo, this study emphasizes the great value of conveying one's confidence in the treatment to bolster its effect (LOE = 2b)
Reference: *Carvalho C, Caetano JM, Cunha L, et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain 2016;157(12):2766-2772.*

#21: Aspirin therapy started early in pregnancy reduces risks of preeclampsia and fetal growth restriction

Clinical question: Does aspirin use in pregnancy reduce complications?
Study design: Meta-analysis (randomized controlled trials)
Funding source: Foundation
Setting: Various (meta-analysis)
Synopsis: This was a well-designed meta-analysis of randomized controlled trials to evaluate the impact of aspirin use in pregnancy. The researchers included 45 studies with 20,909 participants. Studies were generally of good quality and included populations with a high risk for PE (> 7%). One of the inclusion criteria was that participants had been stratified by gestational age at treatment initiation (up to 16 weeks vs 16 weeks or later). Aspirin dosages varied from 50 mg to 150 mg daily. Aspirin was associated with a significant decrease in PE, severe PE, and FGR, with a significant dose-response gradient. A comparison of 100 mg daily aspirin versus 60 mg daily showed that 100 mg was significantly more effective (relative risk [RR] 0.48; 95% CI 0.31 - 0.74 vs RR 0.93; 0.75-1.15). For the subgroup with aspirin therapy started after 16 weeks of gestation there was a significant reduction in PE, but not in severe PE or FGR, and there was no dose-response gradient. Two studies evaluated the combination of dipiridamole (300 mg daily) and aspirin versus control: In a sensitivity analysis that excluded those 2 studies the statistical significance for the beneficial effect of aspirin was marginal (P = .06). A funnel plot analysis showed a likelihood for missing small negative studies, which limits the conclusions for benefit.
Bottom line: This meta-analysis suggests that the use of aspirin starting at or before 16 weeks' gestation at a dose of at least 100 mg reduces the risks of preeclampsia (PE), severe preeclampsia, and fetal growth restriction (FGR). Firm conclusions are limited by potential publication bias and by the fact that when the 2 studies that used aspirin plus dipiridamole were excluded from the analysis the calculated benefit for aspirin alone did not reach statistical significance (P = .06). Combined treatment of aspirin (at a dose of at least 100 mg) and dipiridamole starting before 16 weeks' gestation should be studied further. (LOE = 1b-)
Reference: *Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. Am J Obstet Gynecol 2017;216(2):110-120.*

#22: BP goals in patients older than 60 years

Clinical question: When should treatment be initiated in older patients with hypertension, and what are reasonable goals?
Study design: Practice guideline
Funding source: Foundation
Setting: Various (guideline)
Synopsis: These guidelines were based on a systematic review (doi:10.7326/M16-1754) and were developed by a combined working group representing the American College of Physicians and the American Academy of Family Physicians. The recommendations focus on improving patient-oriented outcomes and are based on graded evidence. The committee represented 2 primary care specialties and members had no reported financial conflicts of interest. For patients older than 60 years the working group strongly recommends a blood pressure target of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events (high-quality evidence), but only after discussion with the patient regarding the benefits and risks of treatment. For patients with a history of stroke or transient ischemic attack, the committee suggests treatment with a goal of 140 mm Hg to reduce the risk for recurrent stroke

(weak recommendation, moderate-quality evidence). For patients at high cardiovascular risk, they similarly suggest a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (weak recommendation, low-quality evidence). The committee provided no recommendations for treating on the basis of diastolic blood pressure, given insufficient evidence, and no recommendations for patients with chronic illnesses, other than as those illnesses affect cardiovascular risk.
Bottom line: Try to remember 60 – 150 – 140. That is: In patients older than 60 years, consider treatment if the systolic blood pressure is 150 mm Hg or higher, or 140 mm Hg or higher in patients with a history of stroke or transient ischemic attack and those at high cardiovascular risk. The guidelines suggest initiating therapy only after a discussion of the benefits and risks with each patient; so, no knee-jerk reactions or mechanical decisions based just on the numbers. The evidence is insufficient to guide therapy on the basis of diastolic blood pressure. (LOE = 5)
Reference: *Qaseem A, Wilt TJ, Rich R, et al, for the Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2017;166:430-437.*

#23: High false-positive rate with lung cancer screening

Clinical question: What can patients expect when they undergo computed tomography to screen for lung cancer?
Study design: Cohort (prospective)
Funding source: Government
Setting: Outpatient (primary care)
Synopsis: This study was conducted in 8 academic medical centers among 93,033 primary care patients. From this group (96.3% of whom were men), the researchers identified 4246 current or former (quit date less than 15 years ago) cigarette smokers who had smoked a minimum of 30 pack-years and invited them to be screened for lung cancer using low-dose CT. Of these, 2106 patients had the screening CT. Overall, 1257 screened patients (59.7%) had a positive finding, including 1184 patients (56.2%) who had 1 or more nodules that needed to be followed. A total of 73 patients (3.5% of all patients screened) had findings suspicious for possible lung cancer and 31 (1.5%) had that diagnosis confirmed within the following year. So, let's run the numbers: This means that for appropriately screened patients undergoing CT, more than half the patients will have a positive finding and 94% of these patients will need additional follow-up. One patient in 17 will be told they may have lung cancer but only 1 in 42 patients with a positive result will actually have lung cancer. Overall, 97.5% of patients with a positive CT scan will not have lung cancer.
Bottom line: If you are thinking about adding lung cancer screening to your delivery of preventive care, be sure to prepare patients. They are likely to receive a positive result, most of the positive results will not be lung cancer, and 1 in 4 patients will require additional tracking (ie, follow-up scans). In this study, more than half (59.7%) of the current or former smokers screened for lung cancer using low-dose computed tomography (CT) had a positive result of some sort. However, 97.5% of them were falsely positive, and half of the patients who screened positive were identified as needing to undergo additional monitoring. (LOE = 1a)
Reference: *Kinsinger LS, Anderson C, Kim J, et al. Implementation of lung cancer screening in the Veterans Health Administration. JAMA Intern Med 2017;177(3):399-406.*